REMARKS

The Office Action dated November 21, 2006 has been received and reviewed. This response is directed to that action.

Claims 1, 2, 17, 18, 25-27, 78, 82 and 85-87 have been amended. Claims 6, 53, and 83 have been cancelled. Support for the amendments can be found in the throughout the specification, and specifically on page 1, line 2; page 6, lines 7-15; and pages 44 and 45. No new matter is believed to have been added.

The applicants submit herewith an unsigned declaration under 37 C.F.R.§1.132. A fully executed declaration will follow shortly hereafter.

The applicants respectfully request that the rejections be withdrawn based on the foregoing amendments and the following arguments.

Claim Objections

The Examiner objected to claim 2 because the term "acute and chronic" should read "acute or chronic". Claim 2 has been amended accordingly, thus obviating this objection.

The Examiner additionally objected to claim 6 because the term "CD14" should read "soluble CD14". Claim 6 has been cancelled, thus obviating the objection.

Claim Rejections- 35 U.S.C. §112, first paragraph, enablement requirement

The Examiner rejected the pending claims under 35 U.S.C. §112, first paragraph because, according to the Examiner, the specification does not provide proper enablement for the claims. However, the Examiner stated that the specification is enabled for a method

for endotoxin-mediated TNF-α production in acute or chronic heart failure, the method comprising the steps of measuring the level of TNF-α from a blood sample taken from the patent, and administering to the patient a therapeutically effective amount of ursodeoxycholic acid when the levels of TNF-α are elevated.

Accordingly, claims 1,2, 17,18, 21, 25-27 have been amended to claim a method for treating endotoxin-mediated immune activation in acute or chronic heart disease patients by administering a therapeutically effective amount of ursodeoxycholic acid, either alone or in combination with a diuretic. Applicants submit that it is not necessary to measure the level of TNF-α in the blood, because it does not significantly differ between the blood of healthy vs. diseased patients. This is clearly shown in Figure 1.

Moreover, claims 82 and 85-87 have been amended in the same manner as claim 1, and applicants submit, for the reasons stated above, that the specification provides proper enablement for these claims.

The Examiner also stated that a pharmaceutical composition comprising ursodeoxycholic acid and a diuretic is properly enabled by the specification. Accordingly, claim 78 has been amended to claim such a composition.

As further support that the claims are properly enabled, applicants submit herewith an unsigned declaration under 37 C.F.R. §1.132, showing another example of an embodiment of the present invention. A fully executed version of this declaration will follow shortly hereafter.

Based on the amendments and remarks presented above, applicants respectfully request that the Examiner withdraw the rejections according to the enablement requirement of 35 U.S.C. §112.

Claim Rejections- 35 U.S.C. §112, first paragraph, written description requirement

The Examiner rejected claims 1-2, 6, 17-18, 25-27, 53, 78,82-83 and 85-87 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the invention. The Examiner stated that the specification only discloses a method for treating endotoxin-mediated immune activation in acute or chronic heart failure by measuring the level of TNF-α, endotoxin or soluble CD14 from a blood sample and administering ursodeoxycholic acid, either alone or in combination with a diuretic.

Accordingly, because the present claims, as amended, are commensurate in scope with the disclosure of the specification, applicants submit the present application satisfies the written description requirement of 35 U.S.C. §112, first paragraph.

Claim Rejections- 35 U.S.C. §112, second paragraph

The Examiner rejected claims 17 and 18 under 35 U.S.C. §112, second paragraph as being indefinite. In claim 17, the Examiner stated that it was not clear which "response" by which "cell" is inhibited. Claim 17 has been amended to clarify that it is the "immune activation" response that is inhibited, thus obviating the rejection.

With regard to claim 18, the Examiner stated that it is not clear which cytokine produced by which cell is being decreased. Applicants submit that the amendment to claim 18 provides added clarity to this issue. Accordingly, applicants respectfully request that the Examiner withdraw the rejections based on 35 U.S.C. §112, second paragraph.

Claim Rejections- 35 U.S.C. §102(b)

The Examiner rejected claims 82-83 under 35 U.S.C. 102(b) as anticipated by US 5,589,358. The Examiner stated that the '358 patent teaches a method for treating liver cirrhosis by administering an effective amount of a bile acid such as ursodeoxycholic acid, and that such a method would inherently reduce the level of LPS in the blood.

The '358 patent relates to the use of an isolated DNA segment encoded for a bile acid co-transporter to treat liver cirrhosis. However, there is no teaching or suggestion in the '358 patent of treating acute or chronic heart failure with ursodeoxycholic acid. Claims 82-83 now relate to a method for treating acute or chronic heart failure, not the treatment of liver cirrhosis. Therefore, the '358 patent does not teach all of the limitations of the present invention.

The Examiner also rejected claims 82-83 and 85 under 35 U.S.C. §102(b) as anticipated by US 5,674,855, stating that the '855 patent teaches a method of treating LPS-induced endotoxemia by administering an effective dose of a bile acid such as cholic acid. Because the claims now specifically recite treating acute or chronic heart failure with deoxycholic acid, applicants submit that the '855 patent does not teach all of the limitations of the present invention, and a *prima facie* case of anticipation can not be established.

Moreover, the Examiner rejected claim 78 under 35 U.S.C. §102(b) as anticipated by US 5,514,696. The Examiner stated that the '696 patent teaches a composition comprising bile acid, diuretics and endothelin, which anticipates a composition comprising bile acid and a diuretic. However, applicants respectfully submit that the Examiner has

misinterpreted the teachings of the '696 patent. Specifically, the patent teaches a composition comprising a diuretic and a "*bile acid sequestrant*", not a bile acid. Applicants submit that a bile acid sequestrant does not anticipate a composition comprising a bile acid, because these substances are clearly distinct. Nonetheless, claim 78 has been amended to limit the composition to ursodeoxycholic acid and a diuretic.

Based on the foregoing amendments and remarks, applicants respectfully request that the rejections based on 35 U.S.C. §102(b) be withdrawn.

Claim Rejections- 35 U.S.C. §103(a)

The Examiner rejected claims 82 and 85-87 under 35 U.S.C. §103(a) as obvious over the '358 patent in view of Gennaro et al (The Science and Practice of Pharmacy). The Examiner stated that the claims differ from the '358 patent only in the method for administering the bile acid, but that Gennaro teaches the different methods for administering pharmaceuticals into the blood stream. As stated above, the claims as amended relate to a method for treating acute or chronic heart failure, while the '358 patent teaches a method for treating liver cirrhosis. Furthermore, there is nothing in the '358 patent that would even suggest using deoxycholic acid to treat heart disease. Accordingly, the applicants respectfully submit that the present invention is not obvious over the '358 patent in view of Gennaro.

The Examiner additionally rejected claims 1-2, 6, 17-18 and 25-27 under 35 U.S.C. §103(a) as obvious over Niebauer et al (Abstract from 71ST Scientific Sessions of the American Heart Association) in view of the '855 patent or Greve et al. (*Hepatology*). The Examiner stated that Niebauer teaches a method for treating chronic heart failure in patients

by measuring the level of cytokine or inflammatory markers such as endotoxin and treating with a diuretic. Niebauer does not, however, teach administering a bile acid. The Examiner stated that it would have been obvious to substitute the diuretic used in Niebauer with the bile acid as taught in the '855 patent, discussed above. Applicants respectfully disagree.

Niebauer teaches that patients with chronic heart failure show elevated endotoxin levels, and that diuretic treatment of these patients results in normalization of endotoxin levels. However, Niebauer does not teach that the endotoxins are the cause of the inflammatory immune activation in chronic heart failure patients. Nor does Niebauer provide any information with regard to the direct relationship between endotoxins and cytokine levels, specifically that a reduction of endotoxin levels is accompanied by a reduction in cytokine levels. Consequently, a person of ordinary skill in the art would not be motivated to combine the teachings of Niebauer and the '855 patent.

Moreover, Greve et al. teaches an in vitro approach for studying the influence of bile acids on endotoxin-induced tumors, and never even suggests using bile acids for treating heart disease.

Additionally, the Examiner rejected claims 21 and 53 under 35 U.S.C. §103(a) as obvious over Niebauer in view of the '855 patent or Greve et al, and further in view of Schwarzenberg et al (Pediatr Res), and claim 1 over Niebauer in view of Bo et al. (Biosci Biotechnol Biochem). Schwarzenberg teaches that LPS can cross the intestinal barrier and that administration of ursodeoxycholic acid can decrease the translocation of LPS and prevent the cytokine response as measured by TNF levels. Bo et al. discloses administering a concentration of bile acid wherein the bile acid such as chenodeoxycholic acid inhibits the inflammatory cytokine production.

However, neither Schwarzenberg nor Bo ever suggests that a bile acid, namely deoxycholic acid, can be used to treat chronic heart disease. Accordingly, applicants submit that neither of these references provide motivation to one of ordinary skill in the art to combine the cited references to achieve a method for treating heart disease by administering ursodeoxycholic acid to a patient.

Based on the amendments and remarks presented above, applicants respectfully request that the Examiner withdraw the rejections and allow this case to proceed to issue. If any issues remain, the resolution of which may be advanced through a telephone conference, the Examiner is invited to contact the applicant's attorney at the number listed below.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefore. The Assistant Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,

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